SCIENTIFIC ABSTRACT

A variety of strategies including mutation compensation, molecular chemotherapy and genetic immunopotentiation have been developed to accomplish gene therapy for cancer. We have developed a novel strategy based upon the intracellular expression of single-chain antibodies (sFv) directed against the erbB-2 oncogene product. Employing this methodology, targeted ablation of the erbB-2 gene product in erbB-2 over-expressing ovarian cancer cells has been accomplished. This has resulted in dramatic alterations of the malignant cellular phenotype in transfected cells in in vitro experiments, resulting in induction of apoptosis and abrogation of tumorigenicity. Additional in vivo studies have confirmed the biologic efficacy of the anti-erbB-2 sFv gene and demonstrated enhance survival in ovarian cancer animal models that are analogous to the human disease. Other preclinical experiments have confirmed the safety of this novel therapeutic in animal models. Thus, this research proposal seeks to develop this method of anti-cancer gene therapy as an experimental therapeutic for patients with ovarian carcinoma, a malignancy commonly diagnosed in advanced stages and associated with a poor prognosis. Specifically, this proposal intends to determine 1) the maximally tolerated single dose, 2) the spectrum of toxicities encountered with, 3) the safety of administration of and, 4) antitumor activity at the molecular level of recombinant adenovirus encoding an anti-erbB-2 single chain antibody gene in previously treated ovarian and extraovarian cancer patients. To achieve these specific aims, this research proposal includes a human gene therapy protocol for ovarian and extraovarian cancer patients with persistent or recurrent disease. A Phase I study will be performed to determine the maximally tolerated dose of this novel therapeutic and its associated clinical toxicity. Safety studies will be performed in the context of these trials to determine if the viral vector employed illicits a host immune response, is expressed in transduced tumor cells, or propagates or replicates in the target cells. Lastly, molecular efficacy studies will be performed to determine if, in the context of human disease, the anti-sFv gene antibody transfects targeted ovarian cancer cells and results in decreased expression of the erbB-2 gene product and decreased cellular proliferation.